

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application.

Listing of Claims

Claim 1 (currently amended) A polynucleotide ~~selected from the group consisting of:~~

~~(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 56, 57, 60, 61, 64, 65, 68, 69, 72, 73, 76, 77, 80, 81, 84, 85, 88, 89, 92, 93, 96, 97, 100, 101, 104, 105, 108, 109, 112, 113, 116, 117, 120, 121, 124, 125, 128, 129, 132, 133, 136, 137, 140, 141, 144, 145, 148, 149, 152, 153, 156, 157, 160, 161, 164, 165, 166, 168, 170, 172, 174 or 176;~~

~~—— (b) a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO: 167, 169, 171, 173, 175 or 177;~~

~~—— (c) a polynucleotide encoding a hPXR polypeptide, wherein said polynucleotide is having at a position corresponding to position 201, 131, 57, 42, 52, 79, 106, 225, 315, 418, 488, 492, 543, 696, 834, 984, 1108, 1308 or 1320 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1), at position corresponding to position 100 or 20 of the hPXR gene (Accession No: gi3769536, wherein the A of the start codon ATG at position 60 has been numbered +1), at a position corresponding to position 29 of Intron 2 of the hPXR gene (Accession No:~~

~~gi3769538, wherein Exon 3 starts at position 477), at a position corresponding to position +72 of Intron 3 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 ends at position 610), at a position corresponding to position +99 of Intron 6 of the hPXR gene (Accession No: gi3769538, wherein Exon 6 ends at position 1216), at a position corresponding to position -73 or -17 of Intron 6 of the hPXR gene (Accession No: gi3769538, wherein Exon 7 starts at position 1217), at a position corresponding to position +36 of Intron 7 of the hPXR gene (Accession No: gi3769538, wherein Exon 7 ends at position 1333) or at a position corresponding to position +43 of Intron 8 of the hPXR gene (Accession No: gi3769538, wherein Exon 8 ends at position 1439) a nucleotide exchange, a nucleotide deletion, an additional nucleotide or a nucleotide deletion and a nucleotide exchange; (d) a polynucleotide encoding a hPXR polypeptide, wherein said polynucleotide is having at a position corresponding to position -201, 131, 52, 106, 418, 834, 1108, 1308 or 1320 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) or at a position corresponding to position +99 of Intron 6 of the hPXR gene (Accession number: gi3769538, wherein Exon 6 ends at position 1216) or at a position corresponding to position +43 of the Intron 8 of the hPXR gene (Accession number: gi3769538, wherein Exon 8 ends at position 1439) an A, at a position corresponding to position -57, 79, 315, 543, 696 or 984 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) or at a position~~

~~corresponding to position 29 of Intron 2 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 starts at position 477), at a position corresponding to position 17 of Intron 6 of the hPXR gene (Accession number: gi3769538, wherein Exon 7 starts at position 1217) or at a position corresponding to position +36 of Intron 7 of the hPXR gene (Accession number: gi3769538, wherein Exon 7 ends at position 1333) a T, at a position corresponding to position 20 of the hPXR gene (Accession number No: gi3769536, wherein the A at the start codon ATG at position 60 has been numbered +1) a deletion, at position corresponding to position 42, 225 or 492 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) a C or at a position corresponding to position 488 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1), at a position corresponding to position 100 of the hPXR gene (Accession No: gi3769536, wherein the A of the start codon ATG at position 60 has been numbered +1), at a position corresponding to position +72 of Intron 3 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 ends at position 610) or at a position corresponding to position 73 of Intron 6 of the hPXR gene (Accession No: gi3769538, wherein Exon 7 starts at position 1217) a G;~~

~~—— (e) a polynucleotide encoding a hPXR polypeptide, wherein said polypeptide comprises an amino acid substitution at position 18, 27, 36, 140, 163 or 370 of the hPXR polypeptide (Accession No: gi3769538, wherein the C of the start codon CTG is at position 280); and~~

~~—— (f) a polynucleotide encoding a hPXR polypeptide, wherein said polypeptide comprises an amino acid substitution of E to K at position 18, of P to S at position 27, of G to R at position 36, of V to M at position 140, of D to G at position 163 or of A to T at position 370 of the hPXR polypeptide (Accession No: gi3769538).~~

Claim 2 (original). The polynucleotide of claim 1, wherein said polynucleotide encodes a variant hPXR protein or fragment thereof.

Claim 3 (original). The polynucleotide of claim 1 or 2, wherein the nucleotide deletion, addition and/or substitution result in altered expression of the hPXR gene compared to the corresponding wild type gene.

Claim 4 (original). A vector comprising the polynucleotide of any one of claims 1 to 3.

Claim 5 (original). The vector of claim 4, wherein the polynucleotide is operatively linked to expression control sequences allowing expression in prokaryotic or eukaryotic cells.

Claim 6 (original). A host cell genetically engineered with the polynucleotide of any one of claims 1 to 3 or the vector of claim 4 or 5.

Claim 7 (original). A method for producing a molecular variant hPXR protein or fragment thereof comprising

- (a) culturing the host cell of claim 6; and
- (b) recovering said protein or fragment from the culture.

Claim 8 (original). A method for producing cells capable of expressing a molecular variant hPXR gene comprising genetically engineering cells with the polynucleotide of any one of claims 1 to 3 or the vector of claim 4 or 5.

Claim 9 (withdrawn). A hPXR protein or fragment thereof encoded by the polynucleotide of any one of claims 1 to 3 or obtainable by the method of claim 7 or from cells produced by the method of claim 8.

Claim 10 (withdrawn). An antibody which binds specifically to the protein of claim 9.

Claim 11 (withdrawn). The antibody of claim 10 which specifically recognizes an epitope containing one or more amino acid substitution(s) as defined in any one of claims 1 to 3.

Claim 12 (withdrawn). A transgenic non-human animal comprising at least one polynucleotide of any one of claims 1 to 3 or the vector of claim 4 or 5.

Claim 13 (withdrawn). The transgenic non-human animal of claim 12 further comprising at least one inactivated wild type allele of the hPXR gene.

Claim 14 (withdrawn). The transgenic non-human animal of claim 12 or 13, which is a mouse or a rat.

Claim 15 (withdrawn). A method of identifying and obtaining a hPXR inhibitor capable of modulating the activity of a molecular variant of the hPXR gene or its gene product comprising the steps of

(a) contacting the protein of claim 9 or a cell expressing a molecular variant hPXR gene comprising a polynucleotide of any one of claims 1 to 3 in the presence of components capable of providing a detectable signal in response to drug metabolism, with a compound to be screened under conditions to permit CYP3A4- or CYP3A7-mediated drug metabolism, and

(b) detecting the presence or absence of a signal or increase of a signal generated from the drug metabolism, wherein the presence or increase of the signal is indicative for a putative inhibitor.

Claim 16 (withdrawn). The method of claim 15 wherein said cell is a cell of claim 6, obtained by the method of claim 8 or is comprised in the transgenic non-human animal of any one of claims 12 to 14.

Claim 17 (withdrawn). A method of identifying and obtaining an hPXR inhibitor capable of modulating the activity of a molecular variant of the hPXR gene product comprising the steps of

- (a) contacting the protein of claim 9 with a first molecule known to be bound by hPXR protein to form a first complex of said protein and said first molecule;
- (b) contacting said first complex with a compound to be screened; and
- (c) measuring whether said compound displaces said first molecule from said first complex.

Claim 18 (withdrawn). The method of claim 17, wherein said measuring step comprises measuring the formation of a second complex of said protein and said compound.

Claim 19 (withdrawn). The method of claim 17 or 18, wherein" said measuring step comprises measuring the amount of said first molecule that is not bound to said protein.

Claim 20 (withdrawn). The method of any one of claim 17 to 19 wherein said first molecule is nifedipine, rifampicine or corticosterone.

Claim 21 (withdrawn). The method of any one of claims 17 to 20 wherein said first molecule is labeled.

Claim 22 (withdrawn). A method of diagnosing a disorder related to the presence of a molecular variant of the hPXR gene or susceptibility to such a disorder comprising

(a) determining the presence of a polynucleotide of any one of claim 1 to 3 in a sample from a subject; and/or

(b) determining the presence of a protein of claim 9.

Claim 23 (withdrawn). The method of claim 22, wherein said disorder is cancer.

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Claim 24 (withdrawn). The method of claim 22 or 23 comprising PCR, ligase chain reaction, restriction digestion, direct sequencing, nucleic acid amplification techniques, hybridization techniques or immunoassays.

Claim 25 (withdrawn). The method of any one of claims 22 to 24, further comprising administering to a subject a medicament to abolish or alleviate said disorder.

Claim 26 (withdrawn). The method of any one of claims 22 to 25, further comprising introducing a functional and expressible wild type hPXR gene into cells.

Claim 27 (withdrawn). A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 15 to 21; and

(c) synthesizing and/or formulating the compound identified and obtained in step (b) in a pharmaceutically acceptable form.

Claim 28 (withdrawn). The method of claim 30, wherein said compound is a drug or prodrug in a form suitable for therapeutic application and preventing or ameliorating the disorder of the subject diagnosed in the method of claim 22 or 23.

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Claim 29 (withdrawn). The method of claim 27 or 28 wherein said compound drug or prodrug is a derivative of a medicament as defined in claim 25.

Claim 30 (withdrawn). An inhibitor identified or obtainable by the method of any one of claims 15 to 21.

Claim 31 (withdrawn). The inhibitor of claim 30 which binds specifically to the protein of claim 9.

Claim 32 (withdrawn). Use of an oligo- or polynucleotide for the detection of a polynucleotide of any one of claims 1 to 3 and/or for genotyping of individual hPXR alleles.

Claim 33 (withdrawn). The use of claim 32 wherein said oligonucleotide is 15 to 50 nucleotides in length and comprises the nucleotide sequence of any one of SEQ ID NOS: 1 to 165 or a complementary sequence.

Claim 34 (currently amended). A primer or probe consisting of an oligonucleotide ~~as defined in claim 33~~ comprising the nucleotide sequence of SEQ ID NO:112 or a complementary sequence.

Claim 35 (withdrawn). Use of an antibody for the detection of the protein of claim 9, the expression of a molecular variant hPXR gene comprising a polynucleotide of any one of claims 1 to 3 and/or for distinguishing hPXR alleles comprising a polynucleotide of any one of claims 1 to 3.

Claim 36 (currently amended). A composition comprising the polynucleotide of any one of claims 1 to 3, the vector of claim 4 or 5, the host cell of claim 6 or obtained by the method of claim 8, ~~the protein of claim 9, the antibody of claim 10 or 11, the inhibitor of claim 30 or the~~ primer or probe of claim 34.

Claim 37 (previously presented). The composition of claim 36 which is a diagnostic or a pharmaceutical composition.